## REMARKS

Reconsideration of the abov -identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-94 are in this case. Claims 1-34, 42, 47, 50, 55, 56 and 61-94 were withdrawn under a restriction requirement as drawn to a non-elected invention. Claims 35-41, 43-46, 48-49, 51-54 and 57-60 have been rejected. Claims 43 and 57 have now been amended. Claims 46 and 60 have now been cancelled. New claims 95 – 99 have now been added.

### *Priority*

The Examiner states that if applicant desires priority under 35 U.S.C. § 119(c) a specific reference to the earlier filed provisional application must be made in the first sentence of the instant specification.

Applicant has amended the specification accordingly to claim benefit of priority of earlier filed U.S. provisional patent applications.

### *35 U.S.C. § 103(a) Rejections*

The Examiner has rejected claims 35-37, 43-46, 48-49, 51 and 57-60 under 35 U.S.C. § 103(a) as being unpatentable over Teufel et al. (US Pat. No. 6,145,511). The Examiner's rejections are respectfully traversed. Claims 43 and 57 have now been amended. Claims 46 and 60 have now been cancelled. New claims 95 – 97 and 99 have now been added.

Teufel et al. disclose a cigarette filter which can contain vitamin B12. The Examiner points out that while Teufel et al. may not specifically state that vitamin B12 is a "hydrocobalamin", it would have been obvious to one having ordinary skill in the art at the time of the invention to utilize hydrocobalamin as the vitamin B12 source since it is well-known that this substance is the naturally occurring and most popular form of the vitamin B12.

The Examiner also points out that vitamin B12 is a well-known antioxidant and therefore would inherently function to reduce or prevent tobacco smoke-

associated loss of peroxidase activity in the aerodigestive tract and/or death of cells in the digestive tract.

The Applicant wishes to point out that the 2003 Sigma catalog describes vitamin B12 (pg. 1014) as cyanocobalamin, while hydroxocobalamin (not "hydrocobalamin" as mistakenly referred to by the Examiner) is designated as vitamin B12a (pg. 528), a molecule which was not described or suggested by Teufel et al.

As is well known in the art, the structure of vitamin B12 is clearly distinct from that of vitamin B12a. Hydroxocobalamin (vitamin B12a) posses a hydroxyl moeity on the active porphyrin ring, while cyanocobalamin (vitamin B12) posses a cyanide moeity at the same position.

This structural difference leads to a substantial functional difference. Hydroxocobalamin (vitamin B12a) is capable of ameliorating tobacco smoke (TS) - associated inactivation of Oral Peroxidase (OPO), a function which cannot be attributed to vitamin B12. As illustrated in Figures 12-13 of the present application, the principle cause of TS associated inactivation of OPO is KCN which is present in the cigarette smoke in significant quantities. It is also illustrated in Figures 14-15 that hydroxocobalamin can effectively reduce the TS or KCN damage to OPO. The hydroxocobalamin molecule facilitates removal of cyanide from TS by replacing the hydroxyl in its porphyrin ring with the cyanide (thereby effectively transforming it into a vitamin B12 molecule) thus preventing damage to the OPO. In sharp contrast, vitamin B12, which was described by the prior art cited by the Examiner, already posses cyanide on the porphyrin ring and thus is incapable of removing cyanide from the TS and therefore incapable of reducing or preventing TS associated inactivation of OPO.

Since the beneficial effect vitamin B12a was neither described nor mentioned by Teufel et al. and since Teufel's invention utilizes vitamin B12 for an entirely different purpose (as an antioxidant), one of ordinary skill in the art would not be motivated to utilize the invention described by Teufel et al. in combination with Vitamin B12a.

Applicant further wishes to point out that the Examiner was incorrect in asserting that an antioxidant agent would be capable of reducing TS inactivation of OPO. As illustrated in Figures 9-11 of the present application, known antioxidants such as ascorbic acid (vitamin C), vitamin E, and glutathione had no effect on reducing TS inactivation of OPO. Evidently, being an antioxidant does not necessarily render a substance capable of protecting OPO from TS-induced inactivation.

Applicant further wishes to point out that the Examiner was incorrect in asserting that an antioxidant agent would be inherently capable of reducing or preventing smoke associated death of cells in the aerodigestive tract. Figure 19 of the present application clearly illustrates that a first antioxidant (reduced glutathione) substantially improved lymphocyte survival in TS-treated saliva while a second antioxidant (ascorbic acid) was ineffective under the same experimental conditions. From these experiments it is abundantly clear that antioxidant capacity does not necessarily render a substance capable of reducing or preventing death of cells in the aerodigestive tract.

Studies of the mechanism involved in TS related cell death in the aerodigestive tract conducted while reducing the present invention to practice uncovered that HCN in cigarette smoke is largely responsible for the inactivation of oral peroxidase. This discovery enables for the first time the selection and/or design of molecules highly suited for protecting oral peroxidase from inactivation by HCN. Accordingly, the teachings of the present application include the use of $CN^-$ chelators to prevent TS-induced inactivation of oral peroxidase, such as described, for example, on page 22 line 23 to page 23 line 1 of the present application. The use of any molecule capable of protecting oral peroxidase from inactivation by HCN has not been described nor suggested by Teufel et al.

Therefore, the teachings of Teufel et al do not guide nor motivate a person skilled in the art, at the time the invention was made, to make the present invention.

The Examiner has rejected claims 38-41, and 52-54 under 35 U.S.C. § 103(a) as being unpatentable over Stavridis et al. (US Pat. No. 5,909,736). The Examiner's rejections are respectfully traversed. New claim 98 has now been added.

Stavridis et al. disclose a cigarette filter enriched with biological substances that are capable of withholding the compounds which are responsible for the damaging effect of cigarette smoke on the respiratory and cardiovascular system. The Examiner points out that Stavridis teaches that treatment of animals with the iron chelator, deferoxamine, has been known to suppress the development of lung injury. The Examiner asserts that it would have been obvious to include deferoxamine the cigarette filter of Stavridis, in order to reduce the damage of cigarette smoke to the respiratory system. The Examiner further asserts that the use of this compound would also, inherently, prevent death of cells in the digestive tract.

Applicant wishes to point out that Stavridis teaches use of a filter enriched with biological substances that are capable of withholding noxious compounds contained in cigarette smoke. Accordingly, suitable biological substances are those selected capable of retaining the noxious compounds in the filter.

In sharp contrast to Stavridis, the instant application teaches and claims the use of "a ...filter being designed and configured so as to enable release of said agent therefrom when in use by the subject" (claim 38). The release of the active agent from the filter is required, according to the present invention, in order to deliver the active agent, via inhalation, to the aerodigestive tract saliva, thereby preventing salivary-mediated damage caused by TS. Accordingly, suitable agents are selected capable of being released from the filter when in use by the subject, as well as being capable of preventing or reducing salivary-mediated damage to cells caused by tobacco smoke. Clearly, the teaching of Stavridis is irrelevant to claims 38-41 of the present application and thus would not guide nor motivate one of ordinary skill in the art to make the present invention.

Applicant further wishes to further point out that Stavridis et al. do not teach or suggest using deferoxamine, or any other iron chelaor, for use in a cigarette filter. Deferoxamine is mentioned, along with DMSO, as compounds known capable of suppressing lung injury in animals. The mention of these compounds is made only in

the context of making the point that "macrophages are the source of the damage causing NO, $O_2$-, $H_2O_2$ and OH compounds". Deferoxamine as well as DMSO are active only when they are relcased and are incapable of withholding noxious compounds contained in cigarette smoke unless they are released from the filter. Stavridis docs not teach release and neither deferoxamine, nor DMSO are implied or suggested by Stavridis for use in a cigarette filter. In fact, it is the opinion of the Applicant that Stavridis et al. teach against using an iron chelator in a cigarette filter. For example, the text of column 9 linc 1 to column 10 linc 3, describes a complexed iron molecule as the biological substance utilizing the invention. By teaching a cigarette filter having a complexed iron, as opposed to an iron chelator, Stavridis et al clearly rule out the use of an iron chelator, such as deferoxamine, in a cigarette filter.

The Examiner has also rejected claims 43-46, and 57-60 under 35 U.S.C. § 103(a) as being unpatentable over Hersh et al. (US Pat. No. 5,829,449). The Examiner's rejections are respectfully traversed. Claims 43 and 57 have now been amended. Claims 46 and 60 have now been cancelled. New claims 96 and 99 have now been added.

Hersh et al. disclose a composition for inclusion within a cigarette filter which includes glutathione. The Examiner asserts that glutathione, which is an antioxidant, would inherently function to reduce/prevent tobacco smoke-associated death of cells in the aerodigestive tract.

Hersh et al. utilize a composition, such as an antioxidant which is capable of reducing the damage caused directly to cells by TS. In contrast, the present invention utilizes an agent which is selected capable of reducing tobacco-smoke salivary-mediated damage to cells, a feature not described or suggested by Hersh et al.

Nevertheless, in order to expedite prosecution of these claims, Applicant has elected to amend claims 43 and 57 to limit the agent utilized to an iron chelator. Since Hersh et al. do not teach or suggest the use of an iron chelator in a cigarette

filter, it is Applicant's opinion that these claims are patentable with respect to the teachings of Hersh et al.

In view of the above arguments and claim amendments, Applicant believes to have overcome the 35 U.S.C. § 103a rejections.

Therefore it is respectfully submitted that claims 35-41, 43-45, 48-49, 51-54, 57-59 and 95-98 are now in condition for allowance. Prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

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*Encl.:*
One month extension fee; and
Response transmittal fee for 3 added claims.